Remarks

I. Addressing Applicants' Entitlement to Priority Claim.

In the Office action, dated 4 October 2004, the Examiner states the following:

> Note that the parent applications [*sic*] 08501664, upon which priority is claimed fail to provide adequate support under 35 U.S.C. 112 for the instant claims 1, 4, 9, 14-16 and 28-38 amended in the preliminary amendment submitted September 17, 2003 of this application. Thus, the filing date of the instant claims is deemed to be the filing date of 08680719 filing date, 07/11/1996. If applicant disagrees, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the earlier priority applications. Applicant is reminded that such priority for the instant limitations requires written description and enablement under 35 U.S.C. § 112, first paragraph.
>
> In clarifying the priority date of the instant claims, applicant should note or address whether the art rejections are prior to the priority date of the instant claims and whether said art occurred more than one year prior to said priority date. Applicant will note that the art rejections are under both 35 U.S.C. §102(a) and 102(b) because the priority date of the instant claims in question [*sic*]. (Office action, dated 4 October 2004, pages 2-3, fifth paragraph and paragraph bridging pages 2-3, underlining in original.)

The present application is a continuation of U.S. Patent Application No. 09/109,505, filed 2 July 1998, which is a continuation of U.S. Patent Application No. 08/680,719, filed 11 July 1996, which is a continuation-in-part of U.S. Patent Application No. 08/501,664, filed 12 July 1995. It is unclear to applicants why the Examiner has asked for clarification of the priority date of the present claims relative to cited art because (i) all of the art cited in rejections under 35 U.S.C. §103(a) have effective publication dates under either 35 U.S.C. §102(b) or 35 U.S.C. §102(e) (Fox, *et al.,* (U.S. Patent No. 5,405,366, filed 12 November 1992), Janssen, *et al.* (EP 539625, published 5 May 1993), JP 56137899 (published 28 October 1981), and Keusch, *et al.,* (U.S. Patent No. 5,143,071, filed 26 March 1990)); and (ii) the reference cited under the double patenting rejection, U.S. Patent No. 6,735,273, has a 371(c)(1), (2), (4) date of 10 October 2002, which completely disqualifies the reference as prior art at least in view of the priority date of U.S. Patent Application No. 08/680,719 (filed, 11 July 1996).

However, in an effort to facilitate prosecution of the present application, basis for the elements of currently pending claim 1 are set forth relative to the first filed application to

which the present application claims priority, that is, relative to U.S. Patent Application No. 08/501,664, filed 12 July 1995. Claim 1 is the only pending independent claim. Claim 1 is distinguished over the prior art for the reasons discussed herein below. Accordingly, all dependent claims define over the cited prior art at least by virtue of their ultimate dependence on claim 1.

Applicants submit that currently pending claim 1 has clear support in U.S. Patent Application No. 08/501,664 throughout the specification and at least at the following locations (page and line numbers are given in **{brackets}** relative to U.S. Patent Application No. 08/501,664 as filed):

1. (Currently Amended) A hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose, comprising: **{page 5, line 31, to page 6, line 12; and page 14, lines 1-23}**

(a) a gel forming polymer material comprising polymer chains, said polymer material consisting essentially of polyethylene oxide, wherein said polyethylene oxide is present in an amount of about 4.0% to about 40% by weight based on the total weight of the hydrogel; **{page 5, line 31, to page 6, line 32; and originally presented claim 1}**

(b) water in an amount of about 95% or less and more than about 55% based on the total weight of the hydrogel; **{page 2, lines 24-27; page 19, lines 23-27; and Examples 1-3, 5-7}**

(c) an enzyme composition comprising glucose oxidase, said glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel, wherein the glucose oxidase can catalyze a reaction between glucose and oxygen resulting in the generation of hydrogen peroxide; **{page 2, line 30, to page 3, line 4; page 3, lines 17-20; page 9, lines 23-27; and page 22, line 5, to page 24, line 4}**

(d) a chloride salt from about 0.3% to about 2% by weight based on the total weight of the hydrogel; **{page 2, line 29; and page 8, lines 8-28}**

(e) a phosphate buffer in an amount sufficient to maintain a pH in the hydrogel in the range of about pH 6 to about pH 8; and **{page 2, lines 4-6; page 3, lines 5-6; page 7, line 16, to page 8, line 7}**

(f) a structural support embedded in the hydrogel; **{page 3, lines 10-11; and page 10, lines 9-20}**

wherein (i) the hydrogel components are treated to remove electroactive compounds, **{page 12, line 31, to page 13, line 5; page 15, lines 15-19; and page 16, lines 7-10}** (ii) there is cross-linking between the polymer chains comprising the hydrogel, **{page 8, line 29, to page 9, line 7; and page 26, lines 3-10}** and (iii) hydrogen peroxide degradative components of hydrogel are reduced such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised. **{page 3, lines 12-16,**

page 11, lines 23-29; page 12, lines 3-9, page 14, lines 24-33; and page 15, line 30, to page 16, line 6}

II. Addressing The Examiner's Rejections.

1. Rejection of Claims Under 35 U.S.C. §103(a).

A. Rejections of the Claims -- Fox, *et al.*, (U.S. Patent No. 5,405,366) in view of Janssen, *et al.* (EP 539625) further in view of JP 5613789.

The Examiner rejected claims 1, 4, 9, 14-16, and 28-38 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Fox, *et al.,* (U.S. Patent No. 5,405,366) in view of Janssen, *et al.* (EP 539625) further in view of JP 56137899.

All of the claims rejected by the Examiner ultimately depend from independent claim 1. Applicants submit that the Examiner failed to establish a case of *prima facie* obviousness for the reasons presented herein below. The following arguments primarily address the teachings of the references and the assertions of the Examiner with reference to the limitations of independent claim 1. The dependent claims define over the cited prior art based, at a minimum, on their reliance on the limitations of independent claim 1. The teachings of the abstract of JP 56137899 are directed only to the combination of glucose oxidase and mutarotase for the electrochemical detection of glucose concentration. This reference does not overcome any of the shortcomings, addressed below, of the references used by the Examiner in the Examiner's rejections of the independent claim.

In the rejection, the Examiner asserted the following:

> Fox et al. discloses the hydrogel comprising (a) gel forming polymer material such as polyethylene oxide (PEO) known as Polyox in an amount of 3-20% of the total weight within the instant claim (see col. 6 lines 63-68); (b) water in an amount from about 58% to 96% wt of the total weight within the instant claim (see Table XIV at col. 21-22; Table XVI at col. 23 line 28); (c) a pharmacologically active agent; (d) sodium chloride as an electrolyte in an amount of 0.1-10 wt% of the total weight overlapping with the instant claimed range; (e) a phosphate buffer that maintains a pH of the hydrogel in pH of 7 (see col. 21 lines 11-49); (f) a structural support embedded in the hydrogel such as non-woven fabric as instantly claimed to form into patches (see abstract, col. 8 line 65 to col. 9 line 10); (g) a humectant (see col. 4 lines 59-64); (h) a biocide (see col. 8 lines 6-24)...
>
> Fox et al. does not expressly disclose that a pharmacologically active agent in the hydrogel is glucose oxidase or mutarotase enzyme.

> Janssen discloses that [*sic*] hydrogel comprises glucose oxidase wherein glucose oxidase is used as a catalyzer in the reaction of glucose with oxygen to produce hydrogen peroxide, used for the same purpose as the instantly claimed [*sic*] (see abstract and col. 1 lines 22-35; claim 1)...
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a pharmacologically active agent glucose oxidase or mutarotase enzyme, in the hydrogels of Fox et al. (Office action, dated 4 October 2004, pages 3-4.)

M.P.E.P. 2143 (Eighth Edition) sets forth the following criteria for the establishment of *prima facie* obviousness:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, as noted above, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." The cited references do not contain the requisite suggestion or motivation -- contrary to the Examiner's assertion. For example, the reference of Fox, *et al.,* teaches only sensing electrodes "suitable for application to skin in connection with both electrical signal sensing medical electrical apparatus and electrical energy transmitting medical electrical apparatus" as follows:

> The electrode assemblies according to this invention are suitable for application to skin in connection with both electrical signal sensing medical electrical apparatus and electrical energy transmitting medical electrical apparatus, i.e., they can be used both as sensing electrodes and as working electrodes. Examples of "sensing" electrodes are those used in electrocardiogram (ECG), electrooculogram (EOG), electrogastrogram (EGG), surface electromyogram (EMG), electrodermal responses (EDR), electroencephalograms (EEG), visual evoked potential (VEP), and auditory evoked responses (AER). Moreover, because the hydrogels employed therein are biologically inert, the assemblies according to this invention are suited to

> the detection of signals requiring application to or implanted within sensitive areas of the body, such as the cornea in the electroretinograms (ERG), or in body cavities where the materials of conventional assemblies may prove unsatisfactory, such as in the summated electrocochleograms (ECOG) electro-olfactorograms (EOGS) and measuring electrovaginal potentials (EVP).
>
> Examples of "working" electrodes for which the electrode assemblies of this invention can be used are those adapted structurally for TENS, use as a Electro-Surgical Unit (ESU), External Cardiac Pacing (ECP) and for Defibrillation (DEFIB). (Fox, *et al.*, col. 12, lines 20-46.)

The present invention is directed to "[a] hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose" (see the preamble of claim 1). None of the sensing electrodes of Fox, *et al.*, is for **electrochemical detection**; rather, the sensing electrodes of Fox, *et al.*, are passive observers sensing a voltage arising, for example, from muscle contraction -- these electrodes are not involved in electrochemical reactions. The reference of Janssen, *et al.*, on the other hand, teaches "an electrochemical sensor for measuring the glucose content of fluids containing very low oxygen content or no oxygen at all" (Janssen, *et al.*, col. 1, lines 1-4). Accordingly, neither reference contains a motivation to combine their teachings. Applicants submit that fair weight has not been given to what the cited references teach in their entireties. In *Bausch & Lomb v. Barnes-Hind/Hydrocurve* (796 F.2d 443, 230 USPQ 416, Fed. Cir. 1986), the court emphasized the following:

> It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

Further, the Examiner did not completely address the differences between the prior art and the claims at issue. *See, e.g., Graham v. John Deere Co.*, 383 USC 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459, S. C. 1966. The Examiner asserted that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a pharmacologically active agent glucose oxidase or mutarotase enzyme, in the hydrogels of Fox et al." The reference of Fox, *et al.*, as noted by the Examiner, contains no teaching regarding glucose oxidase. Fox, *et al.*, does teach the production of patches, comprising pharmacological agents, for the administration of such pharmacological agents.

For example, Fox, *et al.,* teach the following:

> In the manufacture of the PATCHES [*sic*], pharmacologically active agents such as drugs may be added to the gel when the formulation is prepared and prior to irradiating. Alternatively, the pharmacologically active agent may be incorporated into a hydrogel, which has been crosslinked, by contacting the crosslinked gel with a solution or dispersion of the drug. In a further alternative, the drug can be incorporated into the hydrogel by either of the previously mentioned routes followed by the partial or complete removal of water. A solution or dispersion of the same or different drug may be introduced into the dried hydrogel. The resulting hydrogels can be formed into PATCHES which can be adhesively attached to the skin of a patient for long term transmittal of the active agent to the patient. The amounts of active agents which can be included in the gel can vary from 0-50% of the gel, preferably at least 5%.
>
> Pharmacologically active agents which may be included in the hydrogels include but are not limited to topical analgesics such as benzocaine and phenol, hydrocortisone, camphor, lidocaine, trolamane, salicylate, and the like; narcotics such as morphine and the like; topical-counter irritants such as methyl salicylate and menthol, capsaicane and the like; antiseptics such as chlorhexidine glyconate, and the like; appetite suppressants such as phenylpropanolamine hydrochloride, and the like; asthma relief preparations such as epinephrine hydrochloride, and the like; decongestants such as menthol with camphor and oil of eucalyptus, and the like; preparations including corn, warts and callous removers such as salicylic acid, and the like; non-steroidal anti-inflammatory drugs such as piroxicam, ketoprofen, and the like; wound healing enhancers such as ketanserin, and the like; antihistamines such as terfenadine, and the like; anxiety/stress controllers such as diazepam, and the like; migraine headache preparations such as chlorpromazine, dihydroergotamine. Other pharmacologically active agents which may be employed include but are not limited to cisapride, motilim, risperadone, nicotine, povidone/iodine.
>
> Indeed, large macromolecules such as proteins may also be incorporated into the gels of the present invention. See, for example, Gombotz, W. *et al.,* in Proceed. Intern. Symp. Control. Rel. Bioact. Mater., (1992) 19:108-109, the disclosure of which is incorporated by reference herein. In particular, Gombotz et al. describe the incorporation of the protein, TGF-beta, into various hydrophilic gel formulations by exposing the different gel formulations to aqueous solutions of the protein. (Fox, *et al.,* col. 19, line 55, to col. 21, line 5.)

However, glucose oxidase cannot be considered a pharmacologically active agent. A "pharmaceutical" is defined as "a medicinal drug" (from Merriam-Webster's Medical Desk

Dictionary, copyright 1993).

All of the pharmacologically active agents described by the reference of Fox, *et al.*, are medicinal. To support the combination of references, however, the Examiner asserted that the glucose oxidase of Janssen, *et al.* is just another pharmaceutically active agent to be substituted into the hydrogels of Fox, *et al.* As discussed above, applicants submit that there is no basis to construe that glucose oxidase is a "medicinal drug" in the hydrogels of the present invention. In fact, the reference of Janssen, *et al.*, teaches only "a glucose oxidase (G.O.D.) containing hydrogel layer" (see, for example, Janssen, *et al.*, col. 1, lines 10-11) -- not any pharmaceutically active agents. Fox, *et al.*, on the other hand, only teach pharmaceutically active agents (*e.g.*, see above). Accordingly, contrary to the Examiner's assertion, there is no motivation to combine the teachings of the references of Fox, *et al.*, and Janssen, *et al.*, in order to obtain the compositions of the present invention.

Obviousness cannot be established by combining teachings in the prior art absent some teaching or suggestion in the prior art that the combination be made. *See, e.g., In re Stence*, 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell*, 891 F. 2d 899, 13 USPQ2d 1248 (Fed Cir 1989). As can be seen from the above-presented arguments, the cited references do not contain the teaching or suggestion required to combine the disclosures of the references.

Second, none of the cited references contains a teaching or suggestion regarding an expectation of success relating to the combination proposed by the Examiner. The reference of Fox, *et al.*, contains no teachings concerning electrochemical detection or glucose oxidase. The reference of Janssen, *et al.*, contains no guidance concerning the composition of any hydrogel composition. Janssen, *et al.*, recite the following concerning the hydrogel: "a glucose oxidase (G.O.D.) containing hydrogel layer covering said surface of the substrate respectively the electrodes arranged thereon" (Janssen, *et al.*, col. 1, lines 10-13).

Further, as noted above, the reference of Janssen, *et al.*, contains no teaching or suggestion of pharmacologically active agents for medical use. Applicants submit that glucose oxidase is not pharmacologically active agent for transdermal delivery as are the pharmacological agents of Fox, *et al.* The Examiner has provided no reference teaching that glucose oxidase would act as a pharmacological agent in the hydrogels of the present invention. Accordingly, the cited references taken singly or in combination provide no

expectation of success for the composition retrospectively constructed by the Examiner.

To support the rejection the Examiner asserts the following: "Therefore, one of ordinary skill in the art would have reasonably expected that a known and art-recognized glucose oxidase used as a catalyzer in the reaction of glucose with oxygen to produce hydrogen peroxide, would have the same or substantially similar usefulness in the hydrogels of Fox, *et al*..." (Office action, dated 4 October 2004, page 5). However, the fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that combination. *See, e.g., In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). In the present case, none of the cited references contains such a suggestion of the desirability of the combination set forth by the Examiner.

Third, the cited references do not teach or suggest all the claim limitations. The Examiner has clearly failed to establish a *prima facie* case of obviousness because the Examiner has failed to provide references that teach or suggest at least the following three limitations present in independent claim 1:

> an enzyme composition comprising glucose oxidase, **said glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel,**
> ...
> wherein (i) **the hydrogel components are treated to remove electroactive compounds,** (ii) there is cross-linking between the polymer chains comprising the hydrogel, and (iii) **hydrogen peroxide degradative components of hydrogel are reduced such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised.**

The cited references must teach or suggest all of the claim limitations (*see, e.g.,* M.P.E.P. 2143, Eighth Edition). The hydrogels of the present invention are characterized as comprising **glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel**. The hydrogels of the present invention are characterized in that **the hydrogel components are treated to remove electroactive compounds**. Furthermore, the hydrogels of the present invention are characterized in having reduced hydrogen peroxide degradative components, **such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised**. Fox, *et al.,* and Janssen, *et al.,* considered alone or in combination, do not teach or suggest any of these claim limitations.

These characteristics are important for the electrochemical quantification of glucose, for example, as taught by the present specification:

> However, in a preferred embodiment of the invention the glucose oxidase is present in sufficient amount such that any glucose entering the device is almost immediately contacted with a glucose oxidase enzyme to allow for the break down of the glucose. Stated differently the glucose oxidase is not present in such a small concentration such that large percentage amounts of glucose will be present awaiting the availability of a glucose oxidase enzyme in order to allow for the breakdown of the glucose. (Specification, page 20, lines 3-12.)

> In a preferred embodiment of the invention, the gel components were treated to remove compounds that cause a relatively high background electrical signal. For example, additives in the gel components such as the antioxidants present in commercial polymers are electroactive. Such electroactive compounds may be removed by a clean up procedure such as, but is not limited to, diafiltration on the polymer forming materials. For example, the gel prepared in Example 2 below had a background current of 175 nA before polymer clean up by diafiltration, and a background current of 40 nA after clean up by diafiltration. Background currents were measured at 60 min following application of the 0.6V potential. (Specification, page 36, lines 16-28.)

> The hydrogen peroxide can be detected electrochemically at an appropriate sensor by the release of two electrons producing a current proportional to the hydrogen peroxide concentration. Components of the hydrogel are chosen such that the components do not significantly degrade hydrogen peroxide and adversely affect its quantitation. Preferably, components such as catalase, polyvinyl pyrrolidone (PVP), antioxidants such as BHT and BKA, and other peroxide degradative components are reduced or limited such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised. (Specification, page 17, lines 10-23.)

> The invention is remarkable in that it allows for the detection and measuring of amounts of glucose which are 1,2 or even 3 orders of magnitude less than the concentration of glucose in blood. (Specification, page 17, lines 24-27.)

As described above, contrary to the Examiner's assertion, the combination of references does not teach the hydrogels of the present invention. None of the above-discussed three limitations is described by Fox, *et al.* The reference of Janssen, *et al.,* does nothing to make up for these missing elements of Fox, *et al.,* in that Janssen, *et al.,* do not address the specific compositions of hydrogels other than "a glucose oxidase (G.O.D.)

containing hydrogel layer" (Janssen, *et al.,* col. 1, lines 10-11).

Accordingly, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

See also In re Fine, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988), "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

There is no support in the cited references for the Examiners' assertion that the cited references teach the hydrogel compositions of the present invention.

Finally, the Examiner has ignored the preamble of the claims that is directly related to the three claim limitations discussed above. The preamble of claim 1 is as follows: "A hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose." According to M.P.E.P 2111.02 (Eighth Edition, "Weight of Preamble"):

> "[A] claim preamble has the import that the claim as a whole suggests for it." Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is `necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

None of the cited references teaches or suggests any of the three claim limitations discussed above. In the present claim, the preamble should be read "in the context of the entire claim," including the three limitations discussed above, such that "the claim preamble ... be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

Further, the Examiner has not provided references that teach the limitations of all of the dependent claims, for example, none of the cited references teaches a recombinant glucose oxidase (claim 28), none of the cited references teaches glucose oxidase present in an

amount of about 200 units or more per gram weight of the hydrogel (claim 29), none of the cited references teaches a hydrogel wherein the hydrogen peroxide is not degraded more than 20% in 30 minutes (claim 4), and none of the cited references teaches the claimed surface areas of the hydrogels of the present invention (claims 15, 32, and 33). Regarding the surface areas, the Examiner references Fox, *et al.*, col. 8, lines 60-64 and col. 9, lines 6-10. These references in Fox, *et al.*, are not to surface area rather the teachings refer to area weight (*i.e.*, g/inch^2).

Accordingly, the Examiner's assertions on which the Examiner's conclusion of obviousness rests do not meet any of the three criteria for establishing a *prima facie* case of obviousness as set forth in MPEP 2143. Applicants submit that the Examiner has failed to establish a case of *prima facie* obviousness. First, the cited references do not provide the requisite suggestion or motivation to modify the reference or to combine reference teachings. Second, the cited references do not provide a reasonable expectation of success following the modifications proposed by the Examiner. Finally, the cited references do not teach or suggest all the claim limitations.

In view of the above-presented arguments, applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103.

B. Rejections of the Claims -- Keusch, *et al.*, (U.S. Patent No. 5,143,071) in view of Janssen, *et al.*, (EP 539625) and Fox, *et al.*, (U.S. Patent No. 5,405,366).

The Examiner rejected claims 1, 4, 9, 14-16, and 28-38 under 35 U.S.C. §103(a) asserting that the claims are unpatentable over Keusch, *et al.*, (U.S. Patent No. 5,143,071) in view of Janssen, *et al.*, (EP 539625) and further in view of JP 56137899 and Fox, *et al.* (U.S. Patent No. 5,405,366).

All of the claims rejected by the Examiner ultimately depend from independent claim 1. Applicants submit that the Examiner failed to establish a case of *prima facie* obviousness for the reasons presented herein below. The following arguments primarily address the teachings of the references and the assertions of the Examiner with reference to the limitations of independent claim 1. The dependent claims define over the cited prior art based, at a minimum, on their reliance on the limitations of independent claim 1. The teachings of the abstract of JP 56137899 are directed only to the combination of glucose

oxidase and mutarotase for the electrochemical detection of glucose concentration. This reference does not overcome any of the shortcomings, addressed below, of the references used by the Examiner in the Examiner's rejections of the independent claim.

In the rejection, the Examiner asserted the following:

> Keusch et al. discloses the hydrogel comprising (a) gel forming polymer material such as polyethylene oxide (PEO) known as Polyox in an amount of the total weight within the instant claim (see col. 7 lines 14-20); (b) water in an amount of the total weight within the instant claim; (c) a pharmacologically active agent; (d) sodium chloride as an electrolyte in an amount 0.1-15 wt % of the total weight overlapping with the instant claimed range; (e) the pH of the hydrogel is about 7 since it was used *in vivo*; (f) a structural support embedded in the hydrogel such as non-woven fabric as the instantly claimed to form into patches; (g) a humectant (see col. 4 lines 59-64); (h) a biocide. See col. 1 line 64-col. 2 line 10; col. 6 line 52-col. 10 line 19; col. 11 line 65-col. 17 line 3 [*sic*] ...
>
> Keusch et al. does not expressly disclose that a pharmacologically active agent in the hydrogel is glucose oxidase or mutarotase enzyme, the buffer solution, and the particular cross-linking agent.
>
> Janssen discloses that hydrogel [*sic*] comprises glucose oxidase wherein glucose oxidase is used as a catalyzer in the reaction of glucose with oxygen to produce hydrogen peroxide, used for the same purpose as the instantly claimed [*sic*] (see abstract and col. 1 lines 22-35; claim 1).
>
> It would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a pharmacologically active agent glucose oxidase or mutarotase enzyme, in the hydrogels of Keusch et al. (Office action, dated 4 October 2004, pages 5-6.)

M.P.E.P. 2143 (Eighth Edition) sets forth the following criteria for the establishment of *prima facie* obviousness:

> To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.
>
> The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

First, as noted above, "there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." The cited references do not contain the requisite suggestion or motivation -- contrary to the Examiner's assertion. For example, the reference of Keusch, *et al.,* contains no teaching or suggestion of sensing electrodes useful for electrochemical detection. The reference of Keusch, *et al.,* teaches only sensing electrodes "suitable for application to skin in connection with both electrical signal sensing medical electrical apparatus and electrical energy transmitting medical electrical apparatus" as follows:

> The electrode assemblies according to this invention are suitable for application to skin in connection with both electrical signal sensing medical electrical apparatus and electrical energy transmitting medical electrical apparatus, i.e., they can be used both as sensing electrodes and as working electrodes. Examples of "sensing" electrodes are those used in electrocardiogram (ECG), electrooculogram (EOG), electrogastrogram (EGG), surface electromyogram (EMG), electrodermal responses (EDR), electroensephalograms (EEG), visual evoked potential (VEP), and auditory evoked responses (AER). Moreover, because the hydrogels employed therein are biologically inert, the assemblies according to this invention are suited to the detection of signals requiring application to or implanted within sensitive areas of the body, such as the cornea in the electroretinograms (ERG), or in body cavities where the materials of conventional assemblies may prove unsatisfactory, such as in the summated electro-cochleograms (ECOG) electro-olfactorograms (EOGs) and measuring electrovaginal potentials (EVP).
>
> Examples of "working" electrodes for which the electrode assemblies of this invention can be used are those adapted structurally for Transcutaneous Electrical Nerve Stimulation (TENS), use as a Electro-Surgical Unit (ESU), External Cardiac Pacing (ECP) and for Defibrillation (DEFIB). (Keusch, *et al.,* col. 26, lines 42-68.)

The present invention is directed to "[a] hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose" (see the preamble of claim 1). None of the sensing electrodes of Keusch, *et al.*, is for **electrochemical detection**; rather, the sensing electrodes of Keusch, *et al.*, are passive observers sensing a voltage arising, for example, from muscle contraction --

these electrodes are not involved in electrochemical reactions. The reference of Janssen, *et al.,* on the other hand, teaches "an electrochemical sensor for measuring the glucose content of fluids containing very low oxygen content or no oxygen at all" (Janssen, *et al.,* col. 1, lines 1-4). Accordingly, neither reference contains a motivation to combine their teachings. Applicants submit that fair weight has not been given to what the cited references teach in their entireties. In *Bausch & Lomb v. Barnes-Hind/Hydrocurve* (796 F.2d 443, 230 USPQ 416, Fed. Cir. 1986), the court emphasized the following:

> It is impermissible within the framework of section 103 to pick and choose from any one reference only so much of it as will support a given position to the exclusion of other parts necessary to the full appreciation of what such reference fairly suggests to one skilled in the art.

Further, the Examiner did not completely address the differences between the prior art and the claims at issue. *See, e.g., Graham v. John Deere Co.,* 383 USC 1, 86 S. Ct. 684, 15 L Ed2d 545, 148 USPQ 459, S. C. 1966). The Examiner asserted that "[i]t would have been obvious to a person of ordinary skill in the art at the time the invention was made to employ a pharmacologically active agent glucose oxidase or mutarotase enzyme, in the hydrogels of Keusch et al." (Office action, dated 4 October 2004, page 6.) The reference of Keusch, *et al.,* as noted by the Examiner, contains no teaching regarding glucose oxidase. The reference of Keusch, *et al.,* teaches that the hydrogels are chemically inert (Keusch, *et al.,* col. 9, lines 64-67; and col. 33, lines 20-24). The hydrogels of the present invention, on the other hand, are **not** chemically inert, they comprise a chemical catalyst, *i.e.*, glucose oxidase, that (as noted by the Examiner) "glucose oxidase is used as a catalyzer in the reaction of glucose with oxygen to produce hydrogen peroxide." Modification of a reference that destroys the intent, purpose, or function of the invention described in the reference does not suffice to show technological motivation for making such an alteration. On the contrary, such evidence indicates a **disincentive** to combine references. *See, e.g., In re Gordon*, 733 F2d 900, 221 USPQ 1125 (Fed Cir. 1984).

Accordingly, contrary to the Examiner's assertion, there is no motivation to combine the teachings of the references of Keusch, *et al.,* and Janssen, *et al.,* in order to obtain the compositions of the present invention. Obviousness cannot be established by combining teachings in the prior art absent some teaching or suggestion in the prior art that the

combination be made. *See, e.g., In re Stence*, 828 F. 2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987); *In re Newell*, 891 F. 2d 899, 13 USPQ2d 1248 (Fed Cir 1989). As can be seen from the above-presented arguments, the cited references do not contain the teaching or suggestion required to combine the disclosures of the references. In fact, the teachings of Keusch, *et al.,* provide a **disincentive** to combine: the modification of the hydrogels of Keusch, *et al.,* to include glucose oxidase explicitly **contradicts** the teaching of Keusch, *et al.,* that the disclosed hydrogels are chemically inert.

Second, none of the cited references contains a teaching or suggestion regarding an expectation of success relating to the combination proposed by the Examiner. The reference of Keusch, *et al.,* contains no teachings concerning electrochemical detection, glucose oxidase, or the presence of a buffer. The reference of Janssen, *et al.,* contains no guidance concerning the composition of any hydrogel composition. Janssen, *et al.,* recite the following concerning the hydrogel: "a glucose oxidase (G.O.D.) containing hydrogel layer covering said surface of the substrate respectively the electrodes arranged thereon." (Janssen, *et al.,* col. 1, lines 10-13.)

Accordingly, the cited references taken singly or in combination provide no expectation of success for the composition retrospectively constructed by the Examiner. The fact that references can be combined does not make the combination obvious unless the prior art also contains something to suggest the desirability of that combination. *See, e.g., In re Sernaker*, 702 F.2d 989, 217 USPQ 1 (Fed. Cir. 1983). In the Office action the Examiner stated the following:

> Therefore, one of ordinary skill in the art would have reasonably expected that a known and art-recognized glucose oxidase used as a catalyzer in the reaction of glucose with oxygen to produce hydrogen peroxide, would have the same or substantially similar usefulness in the hydrogels of Keusch, et al... (Office action, dated 4 October 2004, page 7).

However, in the present case, none of the cited references contains such a suggestion of the desirability of the combination set forth by the Examiner. In fact, as noted above, the Examiner's modification of the hydrogels of Keusch, *et al.,* so as to contain glucose oxidase is contrary to the teaching of Keusch, *et al.,* that the disclosed hydrogels are chemically inert.

Further, the reference of Keusch, *et al.,* teaches the following: "The hydrophilic gel is

inert and is not metabolized. It has a normal pH of about 7, which is allowed to 'float' between 6 and 8" (Keusch, *et al.,* col. 28, lines 8-10).

Modifying the hydrogels of Keusch, *et al.,* by adding a buffer is counter to the teaching of Keusch, *et al.,* that the pH is "allowed to 'float.'" No basis for combining the references and no suggestion of the desirability of the present invention are present in any of the cited references. The prior art fails to suggest the desirability of modifying the references to achieve the results of the present invention. *See, e.g., In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

Third, the cited references do not teach or suggest all the claim limitations.

The Examiner has clearly failed to establish a *prima facie* case of obviousness because the Examiner has failed to provide references that teach or suggest at least the following three limitations present in independent claim 1:

> an enzyme composition comprising glucose oxidase, **said glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel,**
> ...
> wherein (i) **the hydrogel components are treated to remove electroactive compounds**, (ii) there is cross-linking between the polymer chains comprising the hydrogel, and (iii) **hydrogen peroxide degradative components of hydrogel are reduced such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised**.

The cited references must teach or suggest all of the claim limitations (*see, e.g.,* M.P.E.P. 2143, Eighth Edition). The hydrogels of the present invention are characterized as comprising **glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel**. The hydrogels of the present invention are characterized in that **the hydrogel components are treated to remove electroactive compounds**. Furthermore, the hydrogels of the present invention are characterized in having reduced hydrogen peroxide degradative components, **such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised**. Keusch, *et al.*, Fox, *et al.,* and Janssen, *et al.,* considered alone or in combination, do not teach or suggest any of these claim limitations.

These characteristics are important for the electrochemical quantification of glucose, for example, as taught by the present specification and already discussed herein above.

As described above, contrary to the Examiner's assertion, the combination of references does not teach the hydrogels of the present invention. None of the above-discussed three limitations is described by Keusch, *et al.,* or Fox, *et al.* The reference of Janssen, *et al.,* does nothing to make up for these missing elements, in that Janssen, *et al.,* do not address the specific compositions of hydrogels other than "a glucose oxidase (G.O.D.) containing hydrogel layer" (Janssen, *et al.,* col. 1, lines 10-11).

Accordingly, the only conclusion supported by the record is that the rejection was made impermissibly using hindsight reconstruction of the invention. As stated by the Court of Appeals for the Federal Circuit "[i]t is impermissible to use the claimed invention as an instruction manual or 'template' to piece together the teachings of the prior art so that the claimed invention is rendered obvious." *In re Fritch*, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992).

See, also, *In re Fine*, 5 USPQ2d 1596, 1600 (Fed. Cir. 1988): "One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."

There is no support in the cited references for the Examiners' assertion that the cited references teach the hydrogel compositions of the present invention.

Finally, the Examiner has ignored the preamble of the claims that is directly related to the three claim limitations discussed above. The preamble of claim 1 is as follows: "A hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose." According to M.P.E.P 2111.02 (Eighth Edition, "Weight of Preamble"):

> "[A] claim preamble has the import that the claim as a whole suggests for it." Bell Communications Research, Inc. v. Vitalink Communications Corp., 55 F.3d 615, 620, 34 USPQ2d 1816, 1820 (Fed. Cir. 1995). "If the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is `necessary to give life, meaning, and vitality' to the claim, then the claim preamble should be construed as if in the balance of the claim." Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

None of the cited references teaches or suggests any of the three claim limitations discussed above. In the present claim, the preamble should be read "in the context of the entire claim," including the three limitations discussed above, such that "the claim preamble

... be construed as if in the balance of the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305, 51 USPQ2d 1161, 1165-66 (Fed. Cir. 1999).

Further, the Examiner has not provided references that teach the limitations of all of the dependent claims, for example, none of the cited references teaches a recombinant glucose oxidase (claim 28), none of the cited references teaches glucose oxidase present in an amount of about 200 units or more per gram weight of the hydrogel (claim 29), none of the cited references teaches a hydrogel wherein the hydrogen peroxide is not degraded more than 20% in 30 minutes (claim 4), and none of the cited references teaches the claimed surface areas of the hydrogels of the present invention (claims 15, 32, and 33). Regarding the surface areas, the Examiner references Keusch, *et al.*, col. 8, lines 60-64 and col. 9, lines 6-10. However, there is no discussion of surface areas at these locations in Keusch, *et al.* Keusch, *et al.*, does not discuss surface area dimensions similar to the presently claimed surface areas.

Accordingly, the Examiner's assertions on which the Examiner's conclusion of obviousness rests do not meet any of the three criteria for establishing a *prima facie* case of obviousness as set forth in MPEP 2143. Applicants submit that the Examiner has failed to establish a case of *prima facie* obviousness. First, the cited references do not provide the requisite suggestion or motivation to modify the reference or to combine reference teachings. Second, the cited references do not provide a reasonable expectation of success following the modifications proposed by the Examiner. Finally, the cited references do not teach or suggest all the claim limitations.

In view of the above-presented arguments, applicants respectfully request withdrawal of the rejection of the claims under 35 U.S.C. §103.

2. Double Patenting Rejection.

The Examiner rejected claims 1, 4, 9, 14-16, and 28-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,735,273, in view of Janssen, *et al.* (EP 539625) further in view of JP 56137899.

Applicants respectfully request clarification of the Examiner's rejection of claims 1, 4, 9, 14-16, and 28-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,735,273. As noted

above, the present application has a filing date well before the effective date of U.S. Patent No. 6,735,273 (*i.e.,* 10 October 2002). The present application is a continuation of U.S. Patent Application No. 09/109,505, filed 2 July 1998, which is a continuation of U.S. Patent Application No. 08/680,719, filed 11 July 1996, which is a continuation-in-part of U.S. Patent Application No. 08/501,664, filed 12 July 1995. Even if applicants rely solely upon the priority provided by U.S. Patent Application No. 08/680,719, filed 11 July 1996, then the present application predates the filing date of the German patent application (filed 29 September 2000) that provides the Foreign Application Priority Data for U.S. Patent No. 6,735,273.

Further, the claims of U.S. Patent No. 6,735,273 are not directed to hydrogels, but rather are directed to an X-ray computed tomography apparatus. Accordingly, applicants respectfully request clarification of this rejection from the Examiner.

Conclusion

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please direct all further communications in this application to:

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If the Examiner notes any further matters which the Examiner believes may be expedited by a telephone interview, the Examiner is requested to contact the undersigned at (650) 599-3591.

Respectfully submitted,

Date: 4 Jan 2005 By: Gary R Fabian

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AMENDMENTS TO THE CLAIMS

(including complete listing of the claims)

1. (Currently Amended) A hydrogel for use in electroosmotic extraction of glucose across skin and electrochemical detection of a signal proportional to an amount or concentration of glucose, comprising:

(a) a gel forming polymer material comprising polymer chains, said polymer material consisting essentially of polyethylene oxide, wherein said polyethylene oxide is present in an amount of about ~~0.5%~~ 4.0% to about 40% by weight based on the total weight of the hydrogel;

(b) water in an amount of about 95% or less and more than about 55% based on the total weight of the hydrogel;

(c) an enzyme composition comprising glucose oxidase, said glucose oxidase present in an amount of from about 10 units to about 5,000 units per gram of the total weight of the hydrogel, wherein the glucose oxidase can catalyze a reaction between glucose and oxygen resulting in the generation of hydrogen peroxide;

(d) a chloride salt from about 0.3% to about 2% by weight based on the total weight of the hydrogel;

(e) a phosphate buffer in an amount sufficient to maintain a pH in the hydrogel in the range of about pH 6 to about pH 8; and

(f) a structural support embedded in the hydrogel;

wherein (i) the hydrogel components are treated to remove electroactive compounds, (ii) there is cross-linking between the polymer chains comprising the hydrogel, and (iii) hydrogen peroxide degradative components of hydrogel are reduced such that quantitation of hydrogen peroxide produced by the glucose oxidase reaction is not compromised.

2-3 (Canceled)

4. (Previously Presented) The hydrogel of claim 1, wherein the hydrogen peroxide is not degraded more than 20% in 30 minutes.

5- 8. (Canceled)

9. (Previously Presented) The hydrogel of claim 1, further comprising a mutarotase enzyme.

10-13 (Canceled)

14. (Previously Presented) The hydrogel of claim 1, characterized by a flat configuration having thickness in a range of about 5 μm to about 60 mils.

15. (Previously Presented) The hydrogel of claim 14, characterized by a first and a second surface area wherein each surface area is in a range of about 0.5 cm^2 to about 10 cm^2 and wherein the hydrogel has a thickness of from about 5 μm to 10 mils.

16. (Currently Amended) The hydrogel of claim 1, wherein the structural support material is a non-woven fabric having an outer parameter configuration and size substantially equal to that of the hydrogel ~~patch~~.

17-27 (Canceled)

28. (Previously Presented) The hydrogel of claim 1, wherein the glucose oxidase is a recombinant glucose oxidase.

29. (Previously Presented) The hydrogel of claim 1, wherein the glucose oxidase is present in an amount of about 200 units or more per gram weight of the hydrogel.

30. (Previously Presented) The hydrogel of claim 1, further comprising a biocide.

31. (Previously Presented) The hydrogel of claim 1, further comprising a humectant.

32. (Previously Presented) The hydrogel of claim 1, wherein said hydrogel has a surface area in the range of about 0.5 cm^2 to about 10 cm^2.

33. (Previously Presented) The hydrogel of claim 32, wherein the hydrogel has a thickness in the range of about 1 mils to about 50 mils.

34. (Previously Presented) The hydrogel of claim 1, wherein said cross-linking is carried out by providing ionizing radiation.

35. (Previously Presented) The hydrogel of claim 34, wherein said radiation is electron beam radiation.

36. (Previously Presented) The hydrogel of claim 1, further comprising a cross-linking agent.

37. (Previously Presented) The hydrogel of claim 36, wherein said cross-linking agent is selected from the group consisting of ethylene glycol methacrylate, triethylene glycol methacrylate, trimethylolpropane trimethacrylate, and N,N'-methylenebisacrylamide.

38. (Previously Presented) The hydrogel of claim 1, wherein the hydrogel (i) comprises an amount of greater than 4% and preferably less than 35% by weight of cross-linked polyethylene oxide having a weight average molecular weight of from about 0.02-6 x 10^6 daltons, and (ii) polymer material is subjected to high energy radiation from about 0.2 to about 5.0 Mrads.